REMARKS

The April 9, 2004 Official Action and references cited therein have been carefully considered. In view of the amendments submitted herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested. This reply is submitted together with a Request for Continued Examination.

Status of the prosecution:

Claims 45, 55-65, 70-78 and 80 are pending and were examined. All rejections from on the basis of prior art, as issued in the previous Office Action, were maintained. The claims stand newly rejected under 35 U.S.C. §112.

Claims 45, 55-58, 70 and 75 remain rejected under 35 U.S.C. §102(b) as allegedly anticipated by any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347).

Claims 45, 58, 60-64, 70 and 72 remain rejected under 35 U.S.C. §102(b) as allegedly anticipated by Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16).

Claims 45, 70-72 and 77 remain rejected under 35 U.S.C. §102(b) as allegedly anticipated by Saal et al. (1991, Fertil. Steril. 56: 225-229) as evidenced by Russo et al. (1990, Br. J. Cancer 62: 2343-2347).

Claims 45 and 70-77 remain rejected under 35 U.S.C. §102(b) as allegedly anticipated by Anapliotou et al. (1996, Fertil. Steril. 66: 305-311) as evidenced by Russo et al. (1990, Br. J. Cancer 62: 2343-2347).

Claim 59 remains rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Silverstein et al. (1994, Cancer 73: 1673-1677, abstract only).

Claim 65 remains rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of Mgbonyebi et al. (1997, Proc. Ann. Meeting Am. Soc. Cancer Res. pp A1977 XP002109660).

Claim 78 remains rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of any one of (1) Platanias et al. (1998, J. Biol. Chem. 273: 5577-5581); (2) Oberg et al. (1989, J. Natl. Cancer Inst. 81: 531-535); (3) Recchia et al. (1998, Clin. Ter. 149: 203-208) or (4) Robinson et al. (1990, Breast Cancer Res. Treat. 15: 95-101.

Claim 80 remains rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347), in view of the Sigma Chemical Co. catalog (1995, page 263).

Claims 45, 55-65, 70-78 and 80 stand newly rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness in the recitation of a method for, *inter alia*, preventing a clinically manifest tumor by administering hCG to a patient who already has a clinically manifest tumor.

Claims 45, 55-65, 70-78 and 80 stand newly rejected under 35 U.S.C. §112, first paragraph, for failing to be adequately supported in the specification for a method of preventing clinically manifest tumors by administering hCG to a patient who already has a clinically manifest tumor.

Claims 45, 63, 64 and 73-75 are amended herein. Claim 45 has been amended to more clearly recite the method of the invention. Claim 45 now calls for a method of treating clinically manifest mammary tumors, comprising: (a) detecting a clinically manifest mammary tumor in a host; (b) administering to the a host a first dose of hGC; and (c) administering to the host one or more subsequent doses of hGC, wherein the first dose and the subsequent doses of hCG are administered in an amount and over a period of time effective to inhibit proliferation of mammary tumor cells, thereby treating the clinically

manifest mammary tumors. Claims 63, 64 and 73-75 have been amended for consistency of language in view of the amendment to claim 45. Support for the amendment to claim 45 may be found throughout the specification, for example, at page 8, lines 5-9 and 14-16 (and associated Figures 2 and 3), page 16, lines 22-25, and Examples 1 and 2. Thus, no new matter has been added. Applicants respectfully assert that the presently amended claims are in condition for allowance, for the reasons set forth below.

The claims as amended are drawn to novel subject matter:

Claims 45, 54-58, 70 and 75 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. (1990, J. Natl. Cancer Inst. 82: 1286-1289) (hereinafter Russo et al. 1990(1)); or (3) Russo et al. (1990, Br. J. Cancer 62: 2343-2347) (hereinafter Russo et al. 1990(2)). According to the examiner, each of Srivastava, Russo et al. 1990(1) and Russo et al. 1990(2) teach "a method of treating/preventing DMBA-induced mammary tumor (non invasive, invasive, carcinoma) by administering 100 IU hCG." The examiner asserts therefore that claim 45 and claims 54-58, 70 and 75, dependent therefrom, are anticipated by the three aforementioned references. Applicants traverse this rejection as applied to the presently amended claims.

None of the cited references discloses a method of treating clinically manifest mammary tumors by detecting the mammary tumor in a host, then initiating and carrying out a dosing regimen of hCG in amounts and for a time effective to inhibit mammary tumor cell proliferation. As mentioned in Applicants' response to the previous Office Action, each of the three cited references discloses a similar experimental protocol (set forth in Fig. 1 of Srivastava et al.; in Fig. 1 of Russo et al. 1990(1) and at 2344 (Materials & Methods) of Russo et al. 1990(2). The protocol calls for: (a) injecting 45 or 50 day-old virgin Sprague-Dawley rats with DMBA (or saline); and (b) 20 or 21 days later, injecting the rats with hCG (or saline) periodically for an ensuing number of days. Thus, in each protocol, only 20 or 21 days elapsed between treatment with the carcinogen and administration of the first dose of hCG. In no instance do any of the three references disclose that tumors were clinically

manifest in the rats at the initiation of hCG treatment. On the contrary, Russo et al. 1990(2) (page 2344, right col., last paragraph and Fig. 1) specifically disclose that animals did not begin developing palpable tumors until six weeks after DMBA injection. Likewise, Russo et al. 1990(1) (Table 1) report a latency period for tumor development in the DMBA + hCG (21 days later) (Group IV) of 49-154 days. From these data it is clear that palpable tumors were not present at 21 days post-DMBA treatment, when hCG was first administered. Similarly, Srivastava et al. report that the earliest finding of a mammary tumor following DMBA administration was at 70 days of age (one animal out of 32 had a tumor). Thus Srivastava et al. also teach that the animals did not possess clinically manifest tumors at the time hCG treatment was initiated at 65 days of age.

With regard to Srivastava et al., the examiner asserts that the claimed method is anticipated because, although tumors were not clinically manifest when the hCG treatments were initiated, tumors did manifest during the course of the hCG therapy. Applicants respectfully assert that this rationale does not apply to the claims as presently amended, because the claims now specifically call for detection of a clinically manifest tumor prior to administration of the first dose of hCG.

Since none of the cited references discloses hCG treatment of hosts wherein clinically manifest tumors are detected prior to initiation of the treatment, and each indeed specifically discloses that clinically manifest tumors were not present at the time hCG treatment was initiated, none of the cited references can be said to disclose the invention as presently claimed in claim 45. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 45, 55-58, 70 and 75 under 35 U.S.C. §102(b) on the basis of those references.

Claims 45, 54, 58, 60-64, 70 and 72 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Grattarola (1976, J. Natl. Cancer Inst. 56: 11-16). According to the examiner, the method taught by Grattarola, i.e., "administering 15,000 IU hCG to advanced breast cancer patients who are either pre-menopausal and post-menopausal, and had undergone surgery," would inherently result in the purpose stated in the preamble of the instant claims, thereby anticipating those claims. Applicants traverse this rejection as applied to the presently amended claims.

As mentioned in Applicants' response to the first Office Action, Grattarola nowhere discloses a method of treating clinically manifest mammary tumors by detecting the mammary tumor in a host, then initiating and carrying out a dosing regimen of hCG in amounts and for a time effective to inhibit mammary tumor cell proliferation. In actuality, the only hCG "treatment" mentioned by Grattarola at all was not even a treatment for mammary tumors – it was instead a means of confirming that the increased testosterone excretion observed in some women following ovariectomy (as an adjunct to mastectomy) was due to gonadotropins (see, e.g., page 11, right col., second full paragraph; left column, second full paragraph *et seq.*). In fact, the only hCG administration reported by Grattarola was to post-mastectomy, post-ovariectomy patients (see, e.g., page 12, left col.), who, by definition, could not have had a clinically manifest mammary tumor at the time, because those tumors had been removed previously by surgery. Moreover, it should be noted that Grattarola nowhere teaches or discloses the use of hCG to treat mammary tumors, whether clinically manifest or not. Grattarola discloses a preferred treatment for breast cancer that comprises ovariectomy (as an adjunct to mastectomy), combined with corticosteroids (see, e.g., page 15, right col., first full paragraph).

The examiner asserts that the claimed method is inherently disclosed by Grattarola because the preamble of claim 45 is not read as a positive limitation of the claimed method. Applicants assert that this rationale also does not apply to the claims as presently amended, because the claims now recite a positive method step of detecting a clinically manifest tumor in a host, and then initiating treatment with hCG.

Because Grattarola does not disclose hCG treatment of hosts having clinically manifest tumors, and indeed does not disclose administration of hCG to treat mammary tumors at all, Grattarola cannot be said to disclose the invention as presently claimed in claim 45. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 45, 58, 60-64, 70 and 72 under 35 U.S.C. §102(b) on the basis of Grattarola.

Claims 45, 70-72 and 77 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Saal et al. (1991, Fertil. Steril. 56: 225-229) as evidenced by Russo et al. 1990(2). Claims 45 and 70-77 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Anapliotou et al. (1996, Fertil. Steril. 66: 305-311) as evidenced by Russo et al. 1990(2). With respect to these grounds of rejection, the examiner asserts that the

rejections should stand until resolution is reached with respect to the allegedly confusing recitiation of "treating or preventing" a clinically manifest tumor in a host who already has a clinically manifest tumor. The claims as presently amended are drawn to a method of treating a clinically manifest mammary tumor, and thus no longer contain the allegedly confusing recitation. Accordingly, this rationale for maintaining the rejections should no longer apply. Applicants therefore request reconsideration and withdrawal of these rejections.

The claims as amended are drawn to non-obvious subject matter:

Claim 59 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1) or (3) Russo et al. 1990(2) in view of Silverstein et al. (1994, Cancer 73: 1673-1677, abstract only). The examiner asserts that any one of the primary references teaches that "hCG has a protective effect against breast cancer," and Silverstein et al. teach that tubular or lobular invasive breast mammary carcinoma is also breast cancer. The examiner asserts that it would therefore have been obvious to one of skill in the art to select patients having the specifically recited stage of breast cancer and administer hCG. Applicants continue to traverse this rejection as applied to the presently amended claims.

In order for a *prima facie* case of obviousness to be established under 35 U.S.C. §103, there must be a motivation in the art to combine the references identified by the examiner. The prior art must suggest the desirability of the claimed invention. The mere fact the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01).

Claim 59 depends from claim 45, which is amended to recite that hCG treatment is initiated following detection of a clinically manifest mammary tumor in a host. As explained above, none of the primary references teaches or suggests this method. Silverstein et al., in teaching that tubular or lobular invasive breast mammary carcinoma is also breast cancer, does not supply the teaching that is clearly absent from the primary references, that is, to treat patients having clinically manifest mammary tumors by initiating and carrying out a regimen

of administration of hCG in amounts and for a period of time effective to inhibit tumor cell proliferation. Thus, since there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 59, the cited references fail to establish a *prima facie* case of obviousness of the claimed invention. Withdrawal of the rejection is therefore requested.

Claim 65 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1); or (3) Russo et al. 1990(2), in view of Mgbonyebi et al. (1997, Proc. Ann. Meeting Am. Soc. Cancer Res. pp A1977 XP002109660). The examiner again asserts that any one of the primary references teaches that hCG has a protective effect against breast cancer, and Mgbonyebi et al. teach that hCG is effective in inhibition of estrogen positive breast cancer cells. The examiner asserts that it would therefore have been obvious to one of skill in the art to detect which breast cancer is estrogen positive and to practice the claimed invention with a reasonable expectation of success. Applicants traverse this rejection as applied to the presently amended claims.

Claim 65 depends from claim 45, which is amended to recite that hCG treatment is initiated following detection of a clinically manifest mammary tumor in a host. As explained above, none of the primary references teaches or suggests this method. Mgbonyebi et al., in teaching that that hCG inhibits growth of estrogen-positive breast cancer cells, does not supply the teaching that is clearly absent from the primary references, that is, to treat patients having clinically manifest mammary tumors by initiating and carrying out a regimen of administration of hCG in amounts and for a period of time effective to inhibit tumor cell proliferation. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 65. Since the references fail to supply the motivation to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention of claim 65, and withdrawal of the rejection is therefore requested.

Claim 78 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1); or (3) Russo et al. 1990(2) in view of any one of (1) Platanias et al. (1998, J. Biol. Chem. 273:

5577-5581); (2) Oberg et al. (1989, J. Natl. Cancer Inst. 81: 531-535); (3) Recchia et al. (1998, Clin. Ter. 149: 203-208) or (4) Robinson et al. (1990, Breast Cancer Res. Treat. 15: 95-101. The primary references were applied as in the other rejections, while the four secondary references were cited for their teaching that Type 1 interferon has anti-tumor activity. According to the examiner, it would have been obvious in view of the cited references to administer Type 1 interferon together with hCG, which is the examiner's view of the subject matter of claim 78.

Applicants traverse this rejection as applied to the claims as presently amended. In view of the amendment to claim 45, dependent claim 78 recites a method comprising administering hCG and Type 1 interferon to a host having a clinically manifest mammary tumor. As stated above, the primary references fail to disclose, teach or suggest a method of treating patients having clinically manifest mammary tumors comprising initiating and carrying out a regimen of administration of hCG in amounts and for a period of time effective to inhibit tumor cell proliferation. The secondary references' teachings of the anti-tumor function of Type 1 interferon do nothing to supply the teaching that is clearly absent from the primary references. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 78. Since the references fail to supply the motivation even to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention of claim 78, and withdrawal of the rejection is therefore requested.

Claim 80 was rejected under 35 U.S.C. §103(a) as allegedly obvious over any one of (1) Srivastava et al. (1997, Carcinogenesis 18: 1799-1808); (2) Russo et al. 1990(1); or (3) Russo et al. 1990(2), in view of the Sigma Chemical Co. catalog (1995, page 263). The primary references again were applied as in the other rejections, while the Sigma catalog was cited for teaching the existence of recombinant hCG According to the examiner, it would have been obvious in view of the cited references to administer r-hCG to treat or prevent mammary tumors.

Applicants again traverse this rejection as applied to the claims as presently amended. In view of the amendment to claim 45, dependent claim 80 recites a method comprising

administering r-hCG to a host having a clinically manifest mammary tumor. As stated above, the primary references fail to disclose, teach or suggest a method of treating patients having clinically manifest mammary tumors comprising initiating and carrying out a regimen of administration of hCG in amounts and for a period of time effective to inhibit tumor cell proliferation. The secondary reference's teaching of r-hCG does nothing to supply the teaching that is absent from the primary references. Again then, there is no suggestion in the cited references, alone or combined, to modify their teachings to arrive at the invention as presently claimed in claim 80. Since the references fail to supply the motivation even to make the invention as claimed, clearly the references also supply no expectation of success in practicing the claimed invention. Accordingly, the cited references fail to establish a *prima facie* case of obviousness of the invention of claim 80, and withdrawal of the rejection is therefore requested.

All requirements of 35 U.S.C. §112 are satisfied:

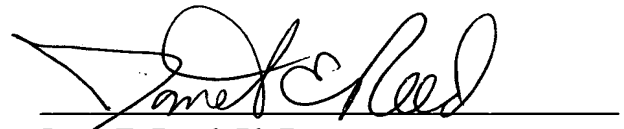
Claims 45, 55-65, 70-78 and 80 stand rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness in the recitation of a method for, *inter alia*, preventing a clinically manifest tumor by administering hCG to a patient who already has a clinically manifest tumor. Claim 45 has been amended to recite a method of treatment, and the recitation of a method of prevention has been removed. Accordingly this rejection should be overcome, and its withdrawal is respectfully requested.

Claims 45, 55-65, 70-78 and 80 stand rejected under 35 U.S.C. §112, first paragraph, for failing to be adequately supported in the specification for a method of preventing clinically manifest tumors by administering hCG to a patient who already has a clinically manifest tumor. As mentioned above, claim 45 has been amended to recite a method of treatment, and the recitation of a method of prevention has been removed. The method recited by the amended claim is more than adequately described in the specification, as discussed above. Accordingly this rejection should be overcome, and its withdrawal is respectfully requested.

Conclusion:

In view of the amendments submitted herewith and the foregoing remarks, the presently pending claims are believed to be in condition for allowance. Applicants respectfully request early and favorable reconsideration and withdrawal of the rejections set forth in the April 9, 2004 Official Action, and allowance of this application.

Respectfully submitted,



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